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Longitudinal (4 year) change of thigh muscle and adipose tissue distribution in chronically painful vs painless knees – data from the Osteoarthritis Initiative

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SUMMARY

Objective: To evaluate 4-year longitudinal change in thigh muscle and adipose tissue content in chronically painful vs painless knees.

Methods: Knees from Osteoarthritis Initiative (OAI) participants with non-acceptable symptom status (numerical rating scale (NRS) ≥4) and frequent pain (≥6 months at baseline, year 2 and year 4 follow-up) were studied. These were matched with painless controls (bilateral NRS pain intensity ≤1 and ≤infrequent pain at all 3 timepoints). 4-year longitudinal changes in thigh muscle anatomical cross-sectional areas (CSAs), isometric muscle strength, and in subcutaneous (SCF) and intermuscular fat (IMF) CSAs were obtained from magnetic resonance images (MRI) and were compared between groups (paired *t*-tests).

Results: 43 participants fulfilled the inclusion criteria of chronic pain, had complete thigh muscle MRI acquisitions and strength measurements, and a matched control. Quadriceps CSAs, but not extensor strength, showed a significant longitudinal decrease in chronically painful knees (−3.9%; 95% confidence interval [95 CI] −6.3%, −1.5%) and in painless controls (−2.4%; 95% CI −4.1%, −0.7%); the difference in change was not statistically significant ($P = 0.33$). There was a significant 4-year gain in SCF in painful knees (8.1%; 95% CI 3.1%, 13%) but not in controls (0.0%; 95% CI −4.4%, +4.4%) with the difference in change being significant ($P = 0.03$). The gain in IMF (~5.2%) was similar between painful and painless knees.

Conclusion: This is the first paper to show a significant impact of (chronic) knee pain on longitudinal change in local subcutaneous adipose tissue. The effect of pain on subcutaneous fat appeared stronger than that on intermuscular adipose tissue and on muscle status.

Introduction

Knee osteoarthritis (KOA) is one of the most common causes of knee pain in the elderly[1] – particularly in obese patients[2,3]. In patients with KOA, low thigh, and particularly quadriceps, muscle strength is commonly observed; this has been associated with limited knee function[4,5] and a further increase in the body mass index (BMI)[6]. Thigh muscle strength, a potentially modifiable risk factor of KOA, has shown to exert beneficial effects on knee pain[7], but thigh muscle strength was apparently not protective of structural (radiographic) progression of KOA[8].

Cross-sectional between-knee, within-person studies suggested that there is no significant relation between radiographic status and thigh muscle strength and did not find smaller quadriceps anatomical cross-sectional areas (CSAs) and extensor strength in limbs with advanced[9] or with early[10] radiographic alterations. In contrast, a strong association was found between knee pain and thigh muscle strength[11,12] with smaller quadriceps CSAs and lower extensor strength found in limbs with frequently painful knees than in contralateral painless limbs[12]. Further, cross-sectional cohort studies in >3000 participants suggested that knee pain, but not radiographic status, was significantly associated with extensor and flexor muscle strength[11], and that extensor and flexor strength both were significantly associated with limb function, as

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assessed by the Western Ontario McMaster Universities (WOMAC) function score[4]. In a first longitudinal study, Beattie *et al.* reported a significant decrease in quadriceps volume and a significant increase in thigh intermuscular fat (IMF) tissue content over 2 years in women with symptomatic KOA; however, the observed change did not exceed that in women without symptoms and radiographic change who had risk factors for KOA[13].

Recent findings suggest that factors other than biomechanics may be involved in the etiology of KOA[14] and these reported associations of pro-inflammatory adipokines (such as leptin) with cartilage degradation[15,16] and with knee pain[17]. However, no study to date has examined the specific impact of (chronic) knee pain on longitudinal change in thigh subcutaneous fat (SCF) tissue content, IMF, muscle CSAs and muscle strength. Given the important relationship between obesity and KOA[2,3] and the potential impact of local (thigh) adipose tissue content on knee pain[18] and function[19], the current study was designed to address the following specific questions:

1) Does 4-year change in thigh muscle CSAs and strength differ between limbs with high intensity chronic knee pain vs those with painless knees?
2) Does 4-year change in thigh SCF and IMF content differ between limbs with high intensity chronic knee pain vs those with painless knees?
3) To what extent are longitudinal changes in SCF and IMF associated with change in muscle CSA and strength, and/or with change in body mass?
4) Do the above longitudinal relationships differ between men and women?
5) Are there cross-sectional differences in thigh muscle, SCF, and IMF CSAs between limbs with high intensity chronic knee pain vs those with painless knees?

Methods

Participants

Participants for this study were drawn from the entire Osteoarthritis Initiative cohort ($n = 4796$; Fig. 1; http://www.oai-ucsf.edu/datarelease/; clinical data sets 0.2.2, 3.2.1, 6.2.2)[20]. Healthy reference cohort participants ($n = 122$) and participants lacking axial thigh muscle MRIs at baseline or year 2 or year 4 follow-up ($n = 2536$) were excluded.

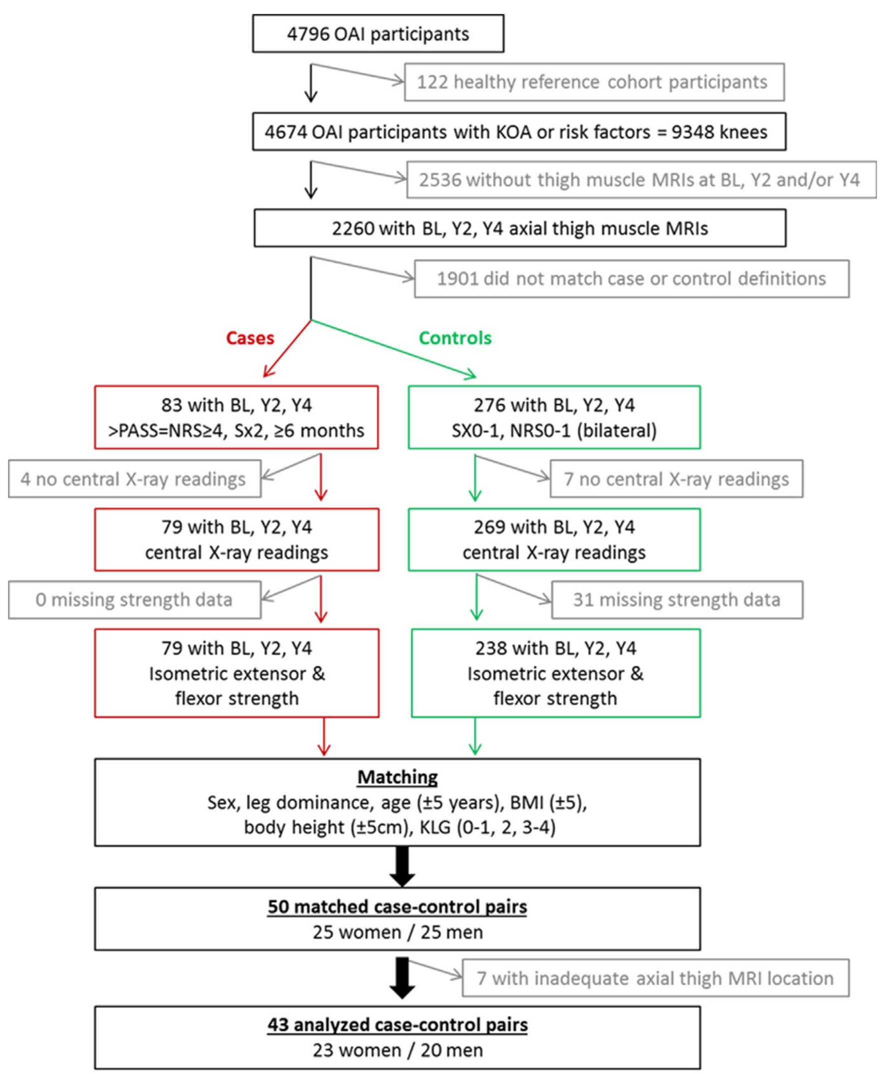

Fig. 1. Process used for selection of participants from the OAI data base. BL = baseline; Y2 = 2-year follow-up; Y4 = 4-year follow-up; PASS = Patient acceptable symptom status; KXSX = pain frequency (0 = no pain; 1 = pain, aching stiffness < half days of a month; 2 = pain aching, stiffness > half days of a month in the last 12 months); NRS = Numeral Rating Scale; BMI = body mass index; KLG = Kellgren–Lawrence grade.

Participants with chronically painful knees (cases) were defined as those with frequent pain (OAI variable KXSX = 2; i.e., pain, aching, stiffness > half days of a month) for at least six months (OAI variable KPNX12M ≥ 6), and with a pain intensity of ≥4 within the last 7 days on the Numerical Rating Scale (NRS; OAI variable P7XKRCV) at all of the above 3 time points (baseline, year 2 and year 4 follow-up). The patient acceptable symptom state (PASS) has been described as the value beyond which patients consider their knee symptoms acceptable[21]. To derive that for patients with KOA, pain was evaluated in 1362 participants with KOA at baseline and 4-week follow-up. The cut-off of the 75% percentile for participants considering themselves as "satisfactory" was 32.3 of 100 mm on the Visual analog scale (VAS)[21]. VAS data were not available in the OAI, and therefore a cut-off of ≥4 on the NRS was chosen to define pain above the PASS[22]. As controls, we selected participants with no or infrequent pain (KXSX = 1; i.e., pain, aching, stiffness < half days of a month in the last 12 months) and with an NRS≤1 in both knees at all of the above three time points. Participants lacking central knee radiographic readings (4 cases; 7 controls) and/or isometric knee extensor and flexor strength data in the OAI data base (none of the cases; n = 33 controls) were excluded.

One limb from each person was used. Participants with a chronically painful knee were matched 1:1 with those with painless knees, based on the same sex, limb dominance (OAI question: "With which leg do you kick a ball"), age (±5years), BMI (±5 kg/m^2), body height (±5 cm), and Kellgren–Lawrence grade (strata of KLG 0–1, 2 or 3–4). Additionally, Physical Activity Scale for the Elderly (PASE) scores (the higher the more activity) were used, as provided by the OAI data base.

Evaluation of thigh muscles, subcutaneous and IMF CSAs from MRI

3T Magnetom Trio magnets (Siemens Health Care) had been used in the OAI for acquiring 15 continuous axial T1-weighted spin-echo images, starting 10 cm proximal to the distal femoral epiphysis (image data sets 0.E.1, 3.E.1, 6.E.1). As described in previous studies[9,10,12], CSAs of the quadriceps, hamstrings, adductors and sartorius muscles were determined by manual segmentation, using an MRI slice at 33% femoral length from distal to proximal (Fig. 2). This location was estimated based on body height and was chosen to account for the variability in body height. Calculations have shown that 33% and 30% of the femoral length can constantly be selected as the most distal and proximal slices throughout participants with different body heights within the OAI, given the specific OAI image acquisition protocol[9,12]. Subcutaneous fat (SCF), intermuscular tissue (IMT), and IMF CSAs were determined in the most proximal slice attainable based on the OAI thigh image acquisition protocol (i.e., 33% of the femoral length from proximal to distal)[18]. SCF, IMT, and IMF were segmented using a semi-automated algorithm which applied a convex "sling" around the muscle tissue. The tissue within this sling, except for femoral corticalis and medulla, was considered IMT (including vessels, nerves etc.). Using a signal intensity threshold IMF was separated from IMT[18]. Further, individual quadriceps heads (vastus medialis [VM], lateralis [VL], intermedius [VIM], and rectus femoris [RF]) were determined in an MRI slice located at 30% femoral length, because separation of the heads is more straight forward distally (Fig. 2)[9,10,12,23]. All segmentations were done in baseline, year 2 and year 4 follow-up images by the same reader (A.R.): The reader was not blinded to the case/control status. The images were processed as triplets, with reference to each other, but the reader was blinded to the order of acquisition throughout the study. Consistency of anatomical locations of selected slices was assured visually. 6 case/control pairs had to be excluded because of incomplete depiction of SCF (n = 2), anatomically inconsistent acquisition of the MRIs that could not be corrected visually (n = 3), and complete substitution of the quadriceps by adipose tissue (n = 1). The total thigh muscle anatomical CSA was calculated as the sum of the individual thigh muscles. The total thigh CSA was calculated as the sum of the thigh muscle CSAs, SCF and IMT CSAs, and total femoral bone CSA (Fig. 2).

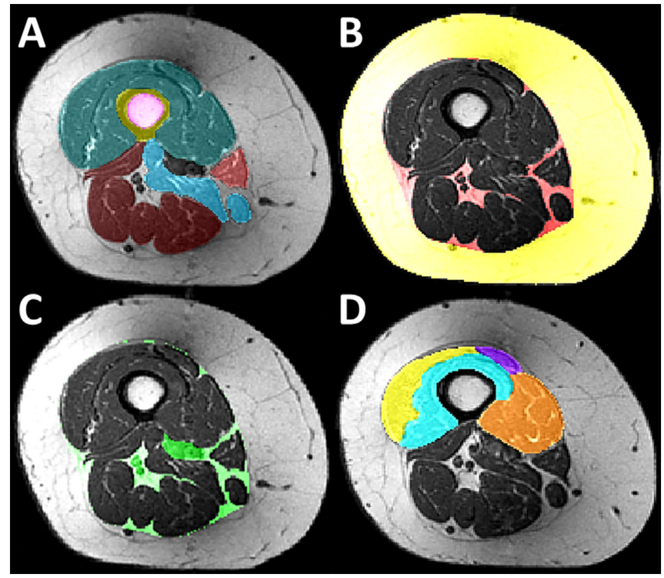

Fig. 2. Axial thigh MRIs with segmentations of A) thigh muscle anatomical ACSAs at 33% of femoral length from distal to proximal of the quadriceps (petrol), hamstrings (red), the adductors (blue), and the Sartorius (pink), and femoral cortex (yellow) with medulla (light pink) = femoral area. B) Segmentations at 33% femoral length of the CSAs of subcutaneous fat (yellow) and IMF (red). C) Segmentation at 33% of femoral length of IMT (green). D) Segmentation at 30% of femoral length of quadriceps head ACSAs of vastus medialis (brown), vastus lateralis (yellow), vastus intermedius (blue), and rectus femoris (purple).

Intra-observer test-retest precision was studied using baseline and year 2 MRI data from OAI healthy reference cohort participants[18]. The root-mean-square coefficient of variation (RMS CV%) for test-retest was 1.3% for quadriceps, 1.1% for hamstrings, and 2.9% for adductor CSAs after a quality control. RMS CV% was 10.7% for SCF, 10.5% for IMT, and 12.4% for IMF[18].

Measurement of maximum thigh isometric muscle strength

Isometric knee extensor and flexor muscle strength measurements were taken from the OAI data base (clinical data sets 0.2.2, 3.2.1, 6.2.2). Strength had been measured using the Good Strength Chair (Metitur Oy, Jyvaskyla, Finland), with the participant sitting in an upright position with flexed hip. The knee was flexed at a defined angle of 60°[9,11,12,24,25]. After three warm-up trials with 50% effort, the highest measurement in isometric strength out of three attempts with 100% effort was determined as the maximum force generated. Specific muscle strength was calculated as extensor strength divided by quadriceps CSA, and flexor strength by hamstring CSA (N/m^2).

Statistical analysis

Absolute and relative (percent) longitudinal changes between baseline to 4-year follow-up changes in thigh tissue composition parameters, muscle (specific) strength, PASE scores, and body mass were determined in cases and in controls. The mean and 95% confidence intervals (CIs) of the longitudinal changes were computed for all measures, in cases and controls respectively, and the significance of the longitudinal change was determined using paired *t*-tests. In view of the matched pair design of the study, the differences in longitudinal changes between cases and controls were also compared using paired *t*-tests.

Given previous reports on the predominant role of the quadriceps muscle in knee biomechanics[26] and on the greater sensitivity to change of muscle CSA vs strength measurements[27], quadriceps CSA change was considered the primary analytic focus in the evaluation of muscle status, whereas measures of muscle strength, and measures of quadriceps head or other thigh muscle CSAs were considered exploratory. No adjustment for parallel testing of quadriceps, SCF and IMF CSA changes was performed, given the exploratory nature of the study. Sensitivity analyses were performed for all analyses, stratifying for sex.

To explore the association of local (thigh) tissue composition with that of systemic (adipose tissue), Pearson-correlation coefficients were computed between the longitudinal changes in quadriceps, SCF, IMF CSAs and body mass in cases. To explore associations between thigh composition parameters and strength Pearson-correlation coefficients between quadriceps, SCF, IMF CSAs and extensor strength using the year 2 follow-up values were calculated.

Finally, cross-sectional differences in all above parameters were calculated between cases and controls using the year 2 follow-up data, in order to relate the current investigation to results of previous cross-sectional studies. To test for a plateau in the change, cross-sectional analyses were re-calculated with baseline data.

Results

79 OAI participants had at least one chronically painful knee, as defined by the study selection criteria as well as thigh MRI acquisitions at baseline, year 2 and year 4 of follow-up (cases) (Fig. 1). 238 OAI participants were bilaterally painless (controls), and had MRI acquisition and strength measurements at all 3 above time points (Fig. 1). Of these, 43 case–control pairs (23 from women; 20 from men) could be matched successfully using the criteria defined in this study, and had MRIs acquired at the required anatomical level and isometric strength measurements available (Fig. 1). Within the cases and controls, 13 knees displayed KLG 0/1 (30%; 6 from women), 13 KLG 2 (30%; 9 from women), and 17 KLG 3/4 (40%; 9 from women). Demographic data for cases and controls at baseline are shown in Table I.

Longitudinal analyses – muscle

Quadriceps CSAs showed a significant longitudinal decrease in limbs with chronically painful knees (−3.9%; 95% CI −6.3%, −1.5%). The observed change was less in painless control limbs (−2.4%; 95% CI −4.1%, −0.7%) but the difference in change between both groups was not significant ($P = 0.33$; Table II). Extensor muscle strength, in contrast, did not show a significant change over time in limbs with either chronically painful or painless knees (Table II). The proportion of the quadriceps CSAs related to the total thigh CSA (including all muscles, adipose, and bone tissue) showed a statistically significantly greater decrease in limbs with chronically painful knees than in those with painless knees ($P = 0.003$) (Table II).

With regard to individual quadriceps heads, the VM and VIM CSAs exhibited statistically significant decreases over 4 years (Table II), with the reduction in VM being greater in limbs with chronically painful than in those with painless knees (−5.8% vs −2.1%, $P = 0.02$; Table II). Changes in the CSAs and strength of other thigh muscles are summarized in Table II.

The sensitivity analyses revealed similar longitudinal changes in limbs from men and women, both in those with chronically painful and in those painless knees, and the above findings did not differ between both sexes (Supplementary Tables 1 and 2).

Longitudinal analyses – adipose tissue

There was a significant 4-year gain in SCF CSAs in limbs with painful knees (8.1%; 95% CI [3.1%, 13.2%]) but not in controls (0.0%; 95% CI [−4.4%, +4.4%]); further, the increase in SCF CSA in limbs with chronically painful knees was statistically significantly greater compared to those with painless knees ($P = 0.03$). The longitudinal gain in IMF, in contrast, was 5.7 vs 4.6% in limbs with painful vs painless knees, and the longitudinal change did not differ between both groups (Table III).

Change in demographic variables and correlation analysis

PASE statistically significantly decreased over the 4 years (Table III) in cases and in controls. No significant change in body mass was observed in the participants with painful or painless knees (Table III).

In chronically painful limbs, there was a positive and statistically significant correlation between 4-year change of SCF CSAs vs change in body mass ($r = 0.72$; 95% CI 0.54, 0.84; $P < 0.001$), and the same applied to IMF change vs body mass change ($r = 0.41$; 95% CI 0.13, 0.64; $P < 0.01$) (Fig. 3). However, the association between change in IMF and SCF CSAs failed to reach statistical significance ($r = 0.30$; 95% CI −0.01, 0.55; $P = 0.054$). There was a significant, positive association of 4-year changes of SCF vs quadriceps CSA ($r = 0.45$; 95% CI 0.17, 0.66; $P < 0.01$), but there was no significant correlation between the IMF CSA change and the quadriceps CSA change ($r = 0.11$; 95% CI −0.20, 0.39; $P = 0.51$) (Fig. 3).

There were statistically significant cross-sectional correlations between quadriceps CSA and knee extensor strength at year 2 for chronically painful ($r = 0.51$; 95% CI 0.25, 0.71; $P < 0.001$) and painless limbs ($r = 0.65$; 95% CI 0.44, 0.80; $P < 0.0001$), respectively and also between SCF and extensor strength ($r = -0.60$; 95% CI −0.76, −0.36; $P < 0.0001$ and $r = -0.32$; 95% CI −0.57, −0.02; $P < 0.05$). In contrast, associations between IMF and knee extensor

Table I
Demographic baseline data for women and men with chronically painful and with painless knees

	Women		Men	
	Chronically painful	Painless	Chronically painful	Painless
	$n = 23$	$n = 23$	$n = 20$	$n = 20$
Age	59.6 ± 9.0	59.9 ± 8.8	62.0 ± 9.0	61.5 ± 8.8
Body height (cm)	162.0 ± 6.0	162.4 ± 5.7	175.7 ± 7.6	177.4 ± 5.9
Body mass (kg)	73.0 ± 9.4	72.8 ± 10.7	87.9 ± 11.9	89.8 ± 13.3
BMI (kg/m^2)	27.9 ± 4.1	27.9 ± 3.9	28.4 ± 2.9	28.4 ± 3.0
PASE	178 ± 73	172 ± 82	190 ± 108	179 ± 73

PASE = Physical Activity Scale for the Elderly, a higher score indicates greater activity.

strength did not attain statistical significance either in chronically painful ($r = -0.23$; 95% CI −0.50, 0.07; $P = 0.13$) nor in painless limbs ($r = 0.13$; 95% CI −0.17, 0.42; $P = 0.40$).

Cross-sectional analyses

Only small cross-sectional differences in quadriceps CSAs were observed between chronically painful vs painless limbs at 2 year follow-up (−2.4%), and these did not attain statistical significance ($P = 0.24$; Table IV). Absolute measures in adipose tissue content also did not differ significantly between painful and painless limbs, but the relative proportion of the quadriceps CSA on the total thigh tissue content appeared to be less in chronically painful compared with painless knees (−3.9%; 95% CI −10.3, 2.4; $P = 0.04$). Also, the VM CSA appeared to be smaller in chronically painful knees compared to painless control knees (Table IV). These results were similar when stratifying by sex or using baseline values (data not shown).

Discussion

To our knowledge, this is the first study to quantitatively evaluate the impact of (chronic) knee pain on longitudinal changes in thigh muscle, subcutaneous and intermuscular adipose tissue CSAs. Given the important associations between obesity and KOA[2,3], not only the effect of a high BMI on the incidence and progression of KOA is of importance in the understanding and management of the disease, but also the impact of knee pain on local (thigh) muscle and adipose tissue composition. We found a significant longitudinal decrease in quadriceps CSA in chronically painful limbs over 4 years that, however, did not significantly exceed the longitudinal decrease in quadriceps muscle in painless controls. SCF CSA, in contrast, showed a significantly greater increase over time in chronically painful than in painless limbs. This increase in SCF caused the relative proportion of quadriceps CSA on the total thigh CSA to decrease more strongly in painful than in painless limbs. These observations were similar for men and women. The longitudinal change of SCF CSA in painful limbs was more strongly correlated with systemic changes of body mass than with local tissue change (i.e., change in muscle CSA). IMF CSA increased with time, but the changes did not differ between painful and painless limbs. Further, IMF CSA changes displayed weaker correlations with weight and quadriceps muscle change than change in SCF CSAs.

A strength of the current study is the relatively long longitudinal observation interval of 4 years, and the comprehensiveness on measures of thigh tissue content and muscle strength being examined. A limitation of the study is the limited sample size, but the cases were very carefully selected from a large cohort to represent limbs with chronic pain. To achieve this, we combined a measure of pain frequency with a measure of pain intensity (the NRS) and the pain status (intensity and frequency) had to be consistent across all 3 time points at which thigh muscle MRIs and muscle strength measurements were taken. Further, knee pain status had to exceed the NRS-level that is considered being acceptable, as described by the PASS[21,22,28]. Since the NRS only covers the last 7 days before visits, we additionally relied on a measure of pain frequency, covering at least 6 months of pain before each of the visits. Data from the OAI healthy reference cohort was unfortunately not available for comparison in this study, because only 26 of the 122 participants had baseline MRI measurements of the thighs, 10 had 2 year data, and none had 4 year longitudinal data. As a control group we therefore selected OAI participants with similar characteristics as the cases, but they had to be (almost) pain-free in both limbs throughout the study. These

Table II
Mean absolute and percent 4-year longitudinal change (and 95% CI) of thigh muscle CSAs, isometric muscle strength and specific strength in chronically painful vs painless knees

	Chronically painful ($n = 43$)		Within group P*	Painless ($n = 43$)		Within group P*	Difference in absolute change	Difference in % change	Between group P†
	Absolute change	% Change		Absolute change	% Change				
Anatomical CSAs **(cm^2)**									
Quadriceps	−2.14 (−3.37, −0.92)	−3.9 (−6.3, −1.5)	0.001	−1.33 (−2.28, −0.39)	−2.4 (−4.1, −0.7)	0.007	−0.81 (−2.48, 0.86)	−1.5 (−4.8, 1.8)	0.33
Quad%TTC	−1.26 (−1.72, −0.81)	−4.8 (−6.6, −3.1)	<0.001	−0.22 (−0.67, 0.24)	−0.8 (−2.4, 0.8)	0.34	−1.05 (−1.71, −0.39)	−4.0 (−6.5, −1.5)	0.003
V. medialis	−1.17 (−1.71, −0.62)	−5.8 (−8.6, −3.0)	<0.001	−0.49 (−0.86, −0.11)	−2.1 (−3.9, −0.3)	0.01	−0.68 (−1.25, −0.11)	−3.7 (−6.6, −0.9)	0.02
V. lateralis	−0.35 (−0.87, 0.17)	−2.2 (−6.3, 1.9)	0.18	−0.19 (−0.61, 0.24)	−0.4 (−3.8, 2.9)	0.39	−0.17 (−0.89, 0.56)	−1.7 (−7.8, 4.3)	0.64
V. intermedius	−0.44 (−0.86, −0.02)	−2.8 (−5.7, 0.1)	0.04	−0.29 (−0.57, −0.01)	−2.1 (−4.1, 0.0)	0.04	−0.15 (−0.69, 0.39)	−0.7 (−4.5, 3.1)	0.58
Rectus femoris	+0.04 (−0.20, 0.28)	+2.7 (−6.5, 11.9)	0.73	−0.07 (−0.20, 0.06)	−2.7 (−8.1, 2.7)	0.31	+0.11 (−0.18, 0.39)	+5.4 (−6.1, 16.8)	0.45
Hamstrings	−1.75 (−2.59, −0.91)	−4.1 (−6.2, −1.9)	<0.001	−1.17 (−1.79, −0.56)	−3.4 (−5.1, −1.6)	<0.001	−0.57 (−1.46, 0.31)	−0.7 (−3.1, 1.7)	0.20
Adductors	+0.44 (−0.63, 1.52)	+7.7 (−1.1, 16.5)	0.41	+0.04 (−0.54, 0.63)	−0.1 (−5.2, 5.0)	0.88	+0.40 (−0.82, 1.63)	+7.8 (−2.5, 18.1)	0.51
Total muscle	−3.47 (−5.90, −1.05)	−2.9 (−5.2, −0.7)	0.01	−2.53 (−4.32, −0.74)	−2.4 (−4.2, −0.7)	0.007	−0.95 (−4.02, 2.13)	−0.5 (−3.4, 2.5)	0.54
Total thigh	+1.70 (−3.34, 6.73)	+1.2 (−1.6, 4.0)	0.50	−2.63 (−6.54, 1.28)	−1.4 (−3.5, 0.7)	0.18	+4.33 (−2.08, 10.7)	+2.6 (−0.9, 6.1)	0.18
Strength (Newton)									
Extensors	−25.6 (−56.1, 4.91)	+5.5 (−15.3, 26.4)	0.10	−22.7 (−49.3, 3.86)	0.0 (−11.0, 11.0)	0.09	−2.86 (−45.5, 39.8)	+5.5 (−18.9, 30.0)	0.89
Flexors	−16.4 (−31.3, −2.36)	+0.2 (−14.3, 14.6)	0.02	−30.8 (−45.4, −16.3)	−10 (−25.9, 5.3)	<0.001	14.0 (−7.03, 35.0)	+10 (−12, 33)	0.19
Specific strength (Newton/cm^2)									
Extensors/Quad	−0.15 (−0.84, 0.53)	+9.6 (−11.4, 30.7)	0.66	−0.31 (−0.81, 0.20)	+2.7 (−9.2, 14.6)	0.23	+0.15 (−0.74, 1.05)	+6.9 (−18, 32)	0.73
Flexors/Ham	−0.22 (−0.63, 0.19)	+5.1 (−10.4, 20.7)	0.28	−0.78 (−1.19, −0.38)	−6.9 (−23.9, 10.0)	<0.001	+0.56 (−0.01, 1.13)	+12 (−12, 37)	0.06

Quad%TTC = percentage of quadriceps of the total thigh cross-sectional area; V. = Vastus; specific strength = isometric strength divided by muscle cross sectional area; Extensors/Quad = Extensors/Quadriceps; Flexors/Ham = Flexors/Hamstrings.

* Paired t-test for change over 4 years.

† Paired t-test comparing change in painful with that in painless knees.

Table III
Absolute and percent 4-year changes (mean with 95% CI) subcutaneous and IMF, and intermuscular tissue CSAs, PASE score, BMI and body weight in chronically painful vs painless knees

	Chronically painful (n = 43)		Within group P*	Painless (n = 43)		Within group P*	Between P group P†
	Absolute change	% Change		Absolute change	% Change		
SCF	+4.69 (1.50, 7.88)	+8.1 (3.1, 13.2)	0.005	−0.08 (−2.88, 2.72)	0.0 (−4.4, 4.4)	0.95	0.03
SCF%TTC	+1.90 (1.08, 2.72)	+6.4 (3.8, 9.0)	<0.001	+0.27 (−0.52, 1.05)	+1.0 (−1.6, 3.6)	0.49	0.006
IMF	+0.45 (0.00, 0.91)	+4.6 (0.5, 8.8)	0.052	+0.51 (0.07, 0.94)	+5.7 (1.3, 10.2)	0.03	0.86
IMF%TTC	+0.21 (−0.03, 0.46)	+3.8 (−0.5, 8.2)	0.09	+0.36 (0.16, 0.56)	+7.3 (3.2, 11.4)	<0.001	0.32
IMT	+0.52 (0.05, 0.99)	+4.0 (0.9, 7.0)	0.03	+0.02 (−0.37, 0.41)	+0.2 (−2.5, 2.9)	0.92	0.08
PASE	−25.6 (−48.8, −2.32)		0.03	−26.0 (−46.9, −5.01)		0.03	0.98
BMI	+0.54 (−0.01, 1.10)	+2.3 (0.1, 4.4)	0.06	−0.01 (−0.52, 0.49)	0.0 (−1.7, 1.7)	0.96	0.13
Body Mass	+1.05 (−0.51, 2.61)	+1.7 (−0.4, 3.8)	0.18	−0.52 (−2.03, 1.00)	−0.4 (−2.1, 1.3)	0.49	0.13

SCF = subcutaneous fat; SCF%TTC = percentage of SCF of the total thigh cross-sectional area; IMF = intermuscular fat; IMF%TTC = percentage of IMF of the total thigh cross-sectional area; IMT = intermuscular tissue; PASE = Physical Activity Scale for the Elderly.
* P for change over 4 years.
† Paired t-test comparing change in painful with that in painless knees.

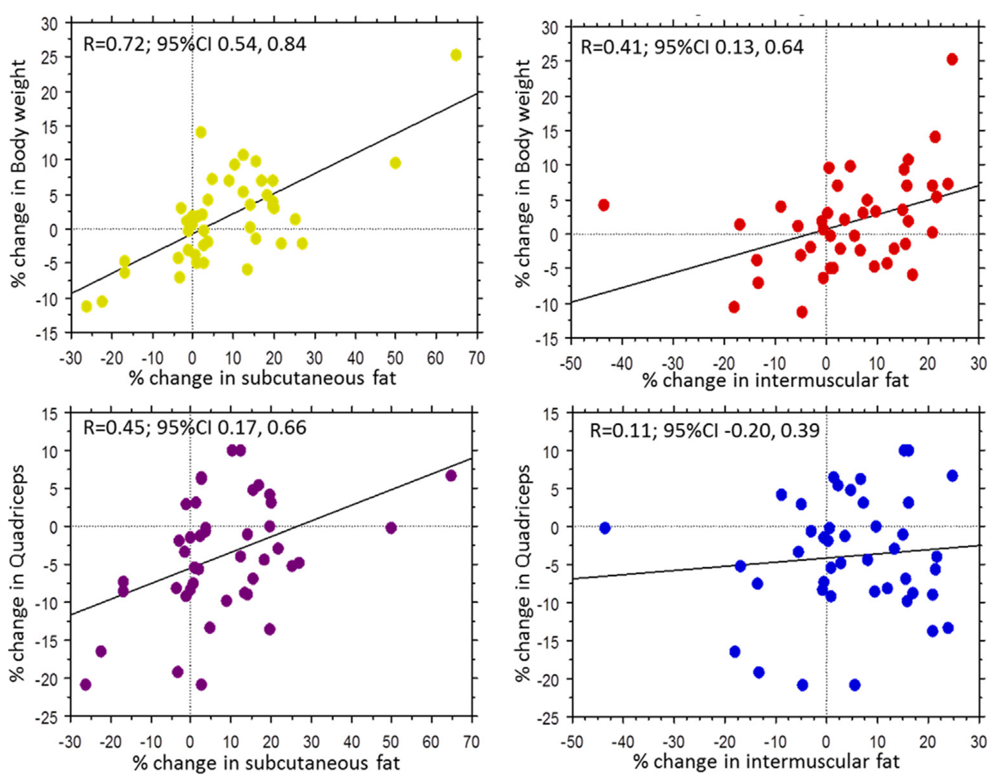

Fig. 3. Scattergrams of 4 year changes (%) of subcutaneous (SCF) and intermuscular fat (IMF cross-sectional areas (CSAs with body weight and with quadriceps CSAs (with correlation coefficients and 95% CI).

were carefully matched 1:1 with cases, to rule out the impact of confounding factors as much as possible.

Although isometric knee extensor strength was reported to be a reliable measure in KOA[29], the current results show a high variability in 4-year changes in thigh muscles strength, which has also been observed in other studies[27,30]. We have shown previously that measurement of quadriceps CSAs is more sensitive to longitudinal change than isometric muscle strength[27], and for this reason, we selected change in quadriceps CSA as the primary outcome of muscle status. Further, determination of muscle CSAs and quadriceps heads have shown to have excellent test-retest reliability[12,23].

There has been good evidence that quadriceps CSAs and strength have a stronger association with knee pain than with the radiographic status of KOA[9,11,12,31,32]. These findings also are supported by a relationship of knee extensor strength with incident knee pain[33,34], and by the beneficial effects of training intervention on knee pain rather than on radiographic progression[35]. However, the effect of (chronic) pain on longitudinal change in thigh muscle strength is unclear: Scott *et al.*[36] reported that women with (any or severe) knee pain at baseline, according to the WOMAC knee pain score, experienced a greater decline in isometric muscle strength over the following 2.6 years than those with no pain at baseline; this observation was, however, not confirmed in men. Using quadriceps CSA as an outcome in participants with continuously high levels of pain, our current study did, in contrast, not identify a difference in the longitudinal relationship of pain and muscle loss between men and women. Beattie *et al.*[13] reported a significant decrease in quadriceps volume over 2 years in women with symptomatic KOA, as defined by baseline pain frequency, which did not differ statistically significantly from that observed in women

Table IV
Mean (±standard deviation) thigh muscle and adipose tissue CSAs, isometric muscle strength, and specific strength and percent differences (mean with 95% CI) between painless and chronically painful knees at the year 2 follow-up

	Chronically painful	Painless	% Difference (95% CI)	Between group *P**
Quadriceps (cm²)	50.4 ± 12.8	52.1 ± 11.7	−2.4 (−8.2, 3.4)	0.24
Quadriceps %TTC	27.0 ± 6.5	28.7 ± 6.5	−3.9 (−10.3, 2.4)	0.04
V. medialis (cm²)	18.7 ± 4.9	20.2 ± 5.3	−5.2 (−12.0, 1.7)	0.04
V. lateralis (cm²)	12.2 ± 4.1	12.9 ± 3.6	−0.4 (−11.5, 10.6)	0.32
V. intermedius (cm²)	14.4 ± 3.8	14.3 ± 3.4	+1.8 (−5.0, 8.5)	0.84
Rectus fem. (cm²)	2.4 ± 1.2	2.1 ± 0.8	+40 (69.5, 11.0)	0.09
Extensors (N)	338 ± 121	364 ± 133	−1.5 (−12.8, 9.7)	0.22
Extensors/Quadriceps (N/cm²)	6.8 ± 2.1	7.0 ± 1.8	+3.2 (−9.1, 15.6)	0.66
Hamstrings (cm²)	35.3 ± 8.6	33.6 ± 7.7	+6.5 (0.3, 12.7)	0.09
Flexors (N)	124 ± 57.1	140 ± 59.8	+10 (−22.9, 43.3)	0.21
Flexors/Hamstrings (N/cm²)	3.6 ± 1.5	4.2 ± 1.4	+4.8 (25.7, 35.2)	0.07
Adductors (cm²)	12.3 ± 5.3	11.0 ± 5.2	+31 (5.9, 56.4)	0.14
SCF (cm²)	65.5 ± 29.4	64.3 ± 36.1	+20 (0.2, 39.7)	0.80
SCF %TTC	34.4 ± 13.2	33.3 ± 14.0	+12 (−1.2, 24.4)	0.51
IMF (cm²)	11.0 ± 3.5	10.6 ± 2.7	+6.5 (−4.1, 17.1)	0.44
IMF%TTC	5.9 ± 1.7	5.8 ± 1.2	+5.4 (−6.1, 16.9)	0.72
IMT (cm²)	14.1 ± 3.7	14.1 ± 3.0	+2.0 (−5.5, 9.5)	0.90
Total thigh (cm²)	188 ± 30.1	185 ± 35.8	+3.7 (−2.2, 9.6)	0.60

95% CI = 95% CI; Quadriceps%TTC = percentage of quadriceps of total thigh cross-sectional area (CSA); Extensors = Extensor strength; N = Newton; Flexors = Flexor strength; SCF = subcutaneous fat; SCF%TTC = percentage of SCF of the total thigh CSA; IMF = intermuscular fat; IMF%TTC = percentage of IMF of the total thigh CSA; IMT = intermuscular tissue.
* Paired *t*-test: chronically painful vs painless at year 2 follow-up.

with risk factors of KOA who did not exhibit frequent pain. Interestingly, the results from our current study reveal very similar rates of change in painful limbs (3.9% over 4 years vs 2.1% over 2 years[13]), and in painless limbs (2.6% over 4 years vs 1.5% over 2 years[13]). This is despite the fact that we selected painful cases as those displaying chronic, unacceptable knee pain at 3 time points spaced over the entire observation period, despite that controls were bilaterally painless, and despite the attempt to match cases and controls 1:1 to rule out other confounders. Taken together, both studies suggest that muscle CSA declines with age and that the effect of (chronic) knee pain on longitudinal change in thigh muscle CSAs is rather limited. This should be interpreted in line with the observation that the activity levels (PASE scores) did show a similar decrease over time in participants with chronically painful and painless knees, and that, surprisingly, the self-assessed activity levels were greater in participants with a chronically painful knee than in those with bilaterally painless knees. A limitation of the study may be that the current sample displayed a relatively low BMI and moderate PASE scores (rather than low scores). Because pain intensity varies based on body mass and physical activity[37], findings may be different in a more sedentary cohort of subjects with KOA. Yet, our findings indicate that greater loss in muscle CSAs in chronically painful knees may occur specifically in the VM, this being in line with previous cross-sectional findings[12,23,38–43]. This finding, however, will have to be confirmed in future longitudinal studies in which the VM CSA being the primary analytic outcome.

Thigh adipose tissue mass has recently been proposed to be more strongly associated with the presence of KOA than skeletal muscle mass, particularly in women[44]. Further, quantitative measures of IMF CSAs have been suspected to be more strongly associated with knee function than muscle mass[19]. However, the presence of chronic pain on longitudinal change of IMF and SCF CSA has not been studied. To achieve this, we relied on a recently developed image analysis approach that was explored in various cross-sectional samples from the OAI, and of which the reliability has been reported[18].

Interestingly, the longitudinal increase in SCF CSAs but not that in IMF CSAs was significantly greater in limbs with chronically painful than in those with painless knees and this applied to men and women. This contrasts to some extent with recent cross-sectional findings of IMF CSAs being larger in frequently painful knees than in contralateral painless knees in women[18]. No significant side differences were, however, identified in SCF CSAs of women, and neither differences of IMF nor SCF CSAs in men[18]. Yet, the cross-sectional component of the current study did not reproduce a significant difference of IMF CSAs between painful and painless knees observed in our previous within-person, between-knee comparison[18]. However, our study confirms and extends findings by Beattie *et al.*[13], who observed no significant difference in the 2-year increase in thigh IMF CSAs in women with symptomatic KOA compared to those with risk factors only[13], and reported similar rates of IMF CSA increase (3.4% over 2 years[13] compared to 5.2% over 4 years in our current study). We, however, did observe an increase in IMT in chronically painful knees. This has to be interpreted with care due to precision errors with segmenting small structures in the context of differentiating between IMT and IMF, e.g., nerves, fibrous tissue and vessels, but may hint to fibrosis of IMT in the presence of chronic knee pain.

Further, the increase in SCF, but not in IMF, was statistically significantly correlated with the decrease in quadriceps CSA. One study previously reported SCF mass to be positively correlated with abduction and extension moments of the knee[45], and this effect was equal to that of abdominal fat mass, despite the smaller SCF content[45]. It has been shown that obesity alters gait and knee kinematics[45–47]. A gain in SCF may lead to greater weight of the thigh and may be responsible for altering hip and knee kinematics to allow the thighs to clear each other during gait; these changes may have unfavorable effects with regard to knee pain. The current observational findings in limbs with chronic pain differ to some extent from those made in an intervention study, in which we found 12 week strength and endurance training to cause a significant increase in quadriceps CSAs, and a concomitant decrease in SCF and IMF CSA in non-trained women without knee pain[48].

In conclusion, the current study shows a significant impact of (chronic) knee pain on longitudinal (4-year) change in subcutaneous adipose tissue, both in men and in women. The impact of chronic pain on change in subcutaneous fat appeared stronger than that on muscle status and that on IMF.

Author's contribution

All authors have made substantial contributions to: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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Role of the funding source

The funding sources took no active part of influence on the analysis of the data and in drafting or revising the article.

Competing interest statement

Felix Eckstein is CEO and co-owner of Chondrometrics GmbH, a company providing MR image analysis services. He provides consulting services to MerckSerono and Mariel Therapeutics, and receives honoraria for educational lectures from Medtronic. Torben Dannhauer has a part-time appointment with Chondrometrics GmbH. Wolfgang Wirth has a part-time appointment with Chondrometrics GmbH and is co-owner of Chondrometrics GmbH. Anja Ruhdorfer has no competing interests.

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Supplementary data

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References

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. AnnRheumDis 2001;60:91–7.
2. Losina E, Walensky RP, Reichmann WM, Holt HL, Gerlovin H, Solomon DH, *et al*. Impact of obesity and knee osteoarthritis on morbidity and mortality in older Americans. AnnInternMed 2011;154:217–26.
3. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham study. AnnInternMed 1988;109:18–24.
4. Ruhdorfer A, Wirth W, Eckstein F. Relationship between isometric thigh muscle strength and minimal clinically important differences (MCIDs) in knee function in osteoarthritis – data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2015 Apr;67(4):509–18.
5. Dijk GM van, Dekker J, Veenhof C, van den Ende CHM. Course of functional status and pain in osteoarthritis of the hip or knee: a systematic review of the literature. Arthritis Rheum 2006;55:779–85.
6. Newman AB, Haggerty CL, Goodpaster B, Harris T, Kritchevsky S, Nevitt M, *et al*. Strength and muscle quality in a well-functioning cohort of older adults: the health, aging and body composition study. J Am Geriatr Soc 2003;51:323–30.
7. Tanaka R, Ozawa J, Kito N, Moriyama H. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. Clin Rehabil 2013;27:1059–71.
8. Bennell KL, Kyriakides M, Metcalf B, Egerton T, Wrigley TV, Hodges PW, *et al*. Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: a randomized controlled trial. Arthritis Rheumatol (Hoboken, NJ) 2014;66:950–9.
9. Ruhdorfer A, Dannhauer T, Wirth W, Hitzl W, Kwoh CK, Guermazi A, *et al*. Thigh muscle cross-sectional areas and strength in advanced versus early painful osteoarthritis: an exploratory between-knee, within-person comparison in osteoarthritis initiative participants. Arthritis Care Res (Hoboken) 2013;65:1034–42.
10. Ruhdorfer AS, Dannhauer T, Wirth W, Cotofana S, Roemer F, Nevitt M, *et al*. Thigh muscle cross-sectional areas and strength in knees with early vs knees without radiographic knee osteoarthritis: a between-knee, within-person comparison. Osteoarthr Cartil 2014;22:1634–8.
11. Ruhdorfer A, Wirth W, Hitzl W, Nevitt M, Eckstein F. Association of thigh muscle strength with knee symptoms and radiographic disease stage of osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2014;66:1344–53.
12. Sattler M, Dannhauer T, Hudelmaier M, Wirth W, Sänger a M, Kwoh CK, *et al*. Side differences of thigh muscle cross-sectional areas and maximal isometric muscle force in bilateral knees with the same radiographic disease stage, but unilateral frequent pain - data from the osteoarthritis initiative. Osteoarthr Cartil 2012;20:532–40.
13. Beattie KA, MacIntyre NJ, Ramadan K, Inglis D, Maly MR. Longitudinal changes in intermuscular fat volume and quadriceps muscle volume in the thighs of women with knee osteoarthritis. Arthritis Care Res (Hoboken) 2012;64:22–9.
14. Griffin TM, Huebner JL, Kraus VB, Guilak F. Extreme obesity due to impaired leptin signaling in mice does not cause knee osteoarthritis. Arthritis Rheum 2009;60:2935–44.
15. Hui W, Litherland GJ, Elias MS, Kitson GI, Cawston TE, Rowan AD, *et al*. Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. AnnRheum Dis 2012;71:455–62.
16. Issa RI, Griffin TM. Pathobiology of obesity and osteoarthritis: integrating biomechanics and inflammation. PathobiolAging Age Relat Dis 2012;2:1–7.
17. Lübbeke A, Finckh A, Puskas GJ, Suva D, Lädermann A, Bas S, *et al*. Do synovial leptin levels correlate with pain in end stage arthritis? Int Orthop 2013;37:2071–9.

18. Dannhauer T, Ruhdorfer A, Wirth W, Eckstein F. Quantitative relationship of thigh adipose tissue with pain, radiographic status, and progression of knee osteoarthritis – longitudinal findings from the osteoarthritis initiative. Invest Radiol 2015 Apr;50(4):268–74.
19. Maly MR, Calder KM, Macintyre NJ, Beattie K a. Relationship of intermuscular fat volume in the thigh with knee extensor strength and physical performance in women at risk of or with knee osteoarthritis. Arthritis Care Res (Hoboken) 2013;65:44–52.
20. Eckstein F, Wirth W, Nevitt MC. Recent advances in osteoarthritis imaging-the Osteoarthritis Initiative. Nat Rev Rheumatol 2012;8:1–9.
21. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64:34–7.
22. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, *et al*. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: results from a prospective multinational study. Arthritis Care Res (Hoboken) 2012;64:1699–707.
23. Sattler M, Dannhauer T, Ring-Dimitriou S, Sänger AM, Wirth W, Hudelmaier M, *et al*. Relative distribution of quadriceps head anatomical cross-sectional areas and volumes-sensitivity to pain and to training intervention. Ann Anat 2014 Dec;196(6):464–70.
24. Rantanen T, Era P, Heikkinen E. Maximal isometric strength and mobility among 75-year-old men and women. Age Ageing 1994;23:132–7.
25. Rantanen T, Era P, Heikkinen E. Physical activity and the changes in maximal isometric strength in men and women from the age of 75 to 80 years. JAmGeriatrSoc 1997;45:1439–45.
26. Segal NA, Glass N a. Is quadriceps muscle weakness a risk factor for incident or progressive knee osteoarthritis? Phys Sportsmed 2011;39:44–50.
27. Dannhauer T, Sattler M, Wirth W, Hunter DJ, Kwoh CK, Eckstein F. Longitudinal sensitivity to change of MRI-based muscle cross-sectional area versus isometric strength analysis in osteoarthritic knees with and without structural progression: pilot data from the osteoarthritis initiative. MAGMA 2014;27:339–47.
28. Pham T, Tubach F. Patient acceptable symptomatic state (PASS). Joint Bone Spine 2009;76:321–3.
29. Tan J, Balci N, Sepici V, Gener FA. Isokinetic and isometric strength in osteoarthrosis of the knee. A comparative study with healthy women. Am J Phys Med Rehabil 1995;74:364–9.
30. Eckstein F, Hitzl W, Duryea J, Kent Kwoh C, Wirth W, Kent KC. Baseline and longitudinal change in isometric muscle strength Prior to radiographic progression in osteoarthritic and Pre-osteoarthritic knees- data from the osteoarthritis initiative. Osteoarthr Cartil 2013;21:682–90.
31. Berger MJ, Kean CO, Goela A, Doherty TJ. Disease severity and knee extensor force in knee osteoarthritis: data from the osteoarthritis initiative. Arthritis Care Res(Hoboken) 2012;64:729–34.
32. Segal NA, Torner JC, Felson D, Niu J, Sharma L, Lewis CE, *et al*. Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. Arthritis Rheum 2009;61:1210–7.
33. Fransen M, Su S, Harmer A, Blyth FM, Naganathan V, Sambrook P, *et al*. A longitudinal study of knee pain in older men: concord health and ageing in men project. Age Ageing 2014;43:206–12.
34. Glass NA, Torner JC, Frey Law LA, Wang K, Yang T, Nevitt MC, *et al*. The relationship between quadriceps muscle weakness and worsening of knee pain in the MOST cohort: a 5-year longitudinal study. Osteoarthr Cartil 2013;21:1154–9.
35. Bennell KL, Hunt MA, Wrigley TV, Lim BW, Hinman RS. Muscle and exercise in the prevention and management of knee osteoarthritis: an internal medicine specialist's guide. MedClinNorth Am 2009;93:161–77. xii.
36. Scott D, Blizzard L, Fell J, Jones G. Prospective study of self-reported pain, radiographic osteoarthritis, sarcopenia progression, and falls risk in community-dwelling older adults. Arthritis Care Res (Hoboken) 2012;64:30–7.
37. Perrot S, Poiraudeau S, Kabir-Ahmadi M, Rannou F. Correlates of pain intensity in men and women with hip and knee osteoarthritis. Results of a national survey: the French ARTHRIX study. Clin J Pain 2009;25:767–72.
38. Elias JJ, Kilambi S, Goerke DR, Cosgarea AJ. Improving vastus medialis obliquus function reduces pressure applied to lateral patellofemoral cartilage. J Orthop Res 2009;27:578–83.
39. Denning WM, Woodland S, Winward JG, Leavitt MG, Parcell AC, Hopkins JT, *et al*. The influence of experimental anterior knee pain during running on electromyography and articular cartilage metabolism. Osteoarthr Cartil 2014;22:1111–9.
40. Hodges PW, Mellor R, Crossley K, Bennell K. Pain induced by injection of hypertonic saline into the infrapatellar fat pad and effect on coordination of the quadriceps muscles. Arthritis Rheum 2009;61:70–7.
41. Fink B, Egl M, Singer J, Fuerst M, Bubenheim M, Neuen-Jacob E. Morphologic changes in the vastus medialis muscle in patients with osteoarthritis of the knee. Arthritis Rheum 2007;56:3626–33.
42. Pattyn E, Verdonk P, Steyaert A, Vanden Bossche L, Van den Broecke W, Thijs Y, *et al*. Vastus medialis obliquus atrophy: does it exist in patellofemoral pain syndrome? Am J Sports Med 2011;39:1450–5.
43. Aminaka N, Pietrosimone BG, Armstrong CW, Meszaros A, Gribble PA. Patellofemoral pain syndrome alters neuromuscular control and kinetics during stair ambulation. J Electromyogr Kinesiol 2011;21:645–51.
44. Visser AW, Mutsert R de, Loef M, le Cessie S, den Heijer M, Bloem JL, *et al*. The role of fat mass and skeletal muscle mass in knee osteoarthritis is different for men and women: the NEO study. Osteoarthr Cartil 2014;22:197–202.
45. Messier SP, Beavers DP, Loeser RF, Carr JJ, Khajanchi S, Legault C, *et al*. Knee joint loading in knee osteoarthritis: influence of abdominal and thigh fat. Med Sci Sports Exerc 2014;46:1677–83.
46. Messier SP, Loeser RF, Hoover JL, Semble EL, Wise CM. Osteoarthritis of the knee: effects on gait, strength, and flexibility. ArchPhysMedRehabil 1992;73:29–36.
47. Runhaar J, Koes BW, Clockaerts S, Bierma-Zeinstra SM. A systematic review on changed biomechanics of lower extremities in obese individuals: a possible role in development of osteoarthritis. ObesRev 2011;12:1071–82.
48. Griessmann S, Dannhauer T, Hudelmaier M, Ruhdorfer A, Wirth W, Himmer M, *et al*. Effects of strength and endurance training intervention on thigh intermuscular and subcutaneous adipose tissue in sarkopenic women. Osteoarhritis Cartil 2014;22(Supplement):S317.